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PRINCIPAL INVESTIGATOR: Michael G. Harrington, M.B., Ch.B., F.R.C.P.

CONTRACTING ORGANIZATION: Huntington Medical Research Institutes
Pasadena, CA 91101

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6. AUTHOR(S)
Michael G. Harrington, M.B., ChB., FRCP.

E-Mail: mghworks@hmri.org

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14. ABSTRACT

The objective of the study is to develop a multimodal approach to assess concussion in the acute phase of injury. This first full year of the project has included several key staff changes, a major instrument acquisition, repairs and upgrades to the MEG, combined with substantial progress with patient recruitment and results that shed light on the primary study goals. We were referred a total of 25 patients from the Hospital, and consented a total of 15 patients, 3 of whom have dropped out. Six with mTBI and six non-head trauma controls have been studied. The first analysis compared acute mTBI patients to non-head trauma controls in the first days after injury. Multiple modalities of behavioral, electrophysiological, and most strikingly, MEG changes were found. The MEG of all mTBI patients had delta activity in the frontal lobes that was absent in all controls. A scientific abstract on these findings has been accepted for publication and these results may be the forerunner of an objective test for acute concussion. Analysis of this data one month after injury when symptoms after mTBI had resolved, is ongoing. This one-month data may provide evidence of neuronal damage recovery from the trauma; objective demonstration of improvement would have exciting potential for predicting and monitoring recovery after acute brain trauma, compared to the persistent delta waves reported in the majority of chronic TBI patients.

15. SUBJECT TERMS
Traumatic brain injury, mTBI, concussion, magnetoencephalography, MEG, MRI, blood biomarkers, actigraphy

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Introduction

The objective of the study is to develop a multimodal approach to assess concussion in the acute phase of injury. Several different measures are included in the assessment. These include functional brain measurement techniques, anatomical brain mapping techniques, biomarkers (blood protein levels), neurocognitive performance (computer-based tests), balance testing, and behavioral health measures. The ultimate aim is to develop an objective method to diagnose mTBI in military personnel proximal to the time of injury and facilitate 'return to duty' decisions.

Keywords

Traumatic brain injury, mTBI, concussion, magnetoencephalography, MEG, MRI, blood biomarkers, actigraphy

Accomplishments

Major Goals

Determine the pattern of physiological and behavioral markers that characterize mild traumatic brain injury (mTBI) to develop a comprehensive methodology for the diagnosis and assessment of this disorder.

Milestones were to consent 50 mTBI patients and 50 non-head trauma controls per year, for 3 multimodal studies within the first month of injury.

Accomplishments

Recruitment in our research project finally started in September 2014. Interactions with the emergency department medical staff have developed successfully based on frequent visits from HMRI to raise awareness. Weekly referrals have been delayed during times of our laboratory down time, due to instrument repairs and personnel absences). We were referred a total of 25 patients from the Hospital, and consented a total of 15 patients, 3 of whom have dropped out. Six with mTBI and six non-head trauma controls have been studied. This patient number that have been compliant with the full study represents accomplishment of 25% of our milestones for the period thus far.

The first analysis compared behavioral and physiological data between acute mTBI patients and non-head trauma controls in the first days after injury. Candidate blood biomarker methods have been developed with femtomole sensitivity for multiple peptides for nine proteins that may arise from brain trauma, using the newly acquired mass spectrometer; analyses are in progress. A larger sample size is required before their analysis. Multiple modalities of behavioral, electrophysiological, and most strikingly, MEG changes have been found in this preliminary study. The MEG of all (n = 6) mTBI patients had delta activity in the frontal lobes that was absent in all controls (n = 6). A scientific abstract on these findings has been accepted for publication and these results may be the forerunner of an objective test for acute concussion. More complete details on the methods, analysis, results, and images are in the

appendix abstract included with this report. Analysis of this same patient group one month after injury when symptoms after mTBI had resolved, is ongoing. This one-month data may provide evidence of neuronal damage recovery from the trauma; objective demonstration of improvement would have exciting potential for predicting and monitoring recovery after acute brain trauma, compared to the persistent delta waves reported in the majority of chronic TBI patients.

Training and Professional Development

Because of the personnel changes, four key personnel acquired critical training as follows:

- Dr. Xianghong Arakaki MD, PhD, is an experienced electrophysiologist but she had not studied human research previously. This year, she has been trained by multiple local and national experts and has become exceedingly proficient at resting EEG, auditory and executive function evoked potentials, and MEG analysis. This has profoundly changed her career direction, in a positive way.
- Ms. Thao Tran is an expert MR spectroscopy and imaging technician and gained expertise at UCSD and UCSF to acquire quality MEG data. She has also trained an HMRI technician, David Strickland, to maintain the MEG instrument and perform routine MEG data acquisition.
- Cherise Charleswell, MPH, had been trained by our local neuropsychology team to administer all of the neuropsychological and behavioral tests.
- The PI required and received intensive training to administer this project, learn the additional components of the science of the project. This was possible only with the extensive support from HMRI, USCD, UCSF, and University of Houston. Dr. Harrington was also required to reduce activities in other research duties to devote additional time to this mTBI project.

Results Dissemination

An abstracted titled “Brain Activation Profiles in mTBI: Evidence from Combined Resting-State EEG and MEG Activity” has been accepted for oral presentation at the 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society to be held in MiCo, Milano Conference Center, Milano, Italy during August 25-29, 2015. Authors Lianyang Li, Mattia Federico Pagnotta, Xianghong Arakaki, Thao Tran, David Strickland, Michael Harrington, George Zouridakis

Plans to Accomplish Goals in Next Reporting Period

We plan to actively continue to recruit mTBI patients and controls and extend the analysis. The highest priority is to compare the clinical improvement of mTBI patients with objective biomarkers; in particular, we plan to closely analyze the MEG delta abnormalities found in all mTBI patients at the 30-day period. We are considering reassessing these patients and controls at an additional time point such as at six months to determine how these MEG observations change. We will seek opinion from our army advisors before making this decision once we have completed the initial 30-day analysis.

Impact

Nothing to report.

Changes/Problems

Major personnel changes in the summer of 2014 included:

- Captain Merrifield left this project in July 2014 and his major role has required considerable adjustments. The unexpected requirements for acquiring at least some of his neurobehavioral and MEG expertise were challenging but have been accomplished.
- Dr. Brian Ross retired in July 2014. He has been a world leading in MR technologies. The essential MR component for this project has been maintained fully by Thao Tran, trained by Dr. Ross.
- Analysis of EEG, MEG, and MRI data with source localization and co-registration has been achieved by a combination of Dr. Arakaki, Ms. Thao Tran, and our external consultant, Dr. George Zouridakis in Houston, Texas.

Products

Nothing to report.

Participants & Other Collaborating Organizations

Name	George Zouridakis
Project Role	Consultant Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-7770-9857
Nearest person month worked	2
Contribution to Project	Analysis of EEG, MEG, and MRI data with source localization and co-registration
Funding Support	Subcontract from HMRI

Name	Lianyang Li
Project Role	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0002-9600-3120
Nearest person month worked	6
Contribution to Project	Analysis of EEG, MEG, and MRI data with source localization and co-registration
Funding Support	Subcontract from HMRI

Special Reporting Requirements

Nothing to report.

Appendices

Accepted abstract from science meeting presentation: EMBC15_mTBI_paper_final_r1a.pdf

Brain Activation Profiles in mTBI: Evidence from Combined Resting-State EEG and MEG Activity

Lianyang Li, Mattia F. Pagnotta, Xianghong Arakaki, Thao Tran, David Strickland, Michael Harrington, and George Zouridakis, *Senior Member, IEEE*

***Abstract*—In this study, we compared the brain activation profiles obtained from resting state Electroencephalographic (EEG) and Magnetoencephalographic (MEG) activity in six mild traumatic brain injury (mTBI) patients and five orthopedic controls, using power spectral density (PSD) analysis. We first estimated intracranial dipolar EEG/MEG sources on a dense grid on the cortical surface and then projected these sources on a standardized atlas with 68 regions of interest (ROIs). Averaging the PSD values of all sources in each ROI across all control subjects resulted in a normative database that was used to convert the PSD values of mTBI patients into z-scores in eight distinct frequency bands. We found that mTBI patients exhibited statistically significant overactivation in the delta, theta, and low alpha bands. Additionally, the MEG modality seemed to better characterize the group of individual subjects. These findings suggest that resting-state EEG/MEG activation maps may be used as specific biomarkers that can help with the diagnosis of and assess the efficacy of intervention in mTBI patients.**

I. Introduction

Mild traumatic brain injury (mTBI) is defined as a transient change in brain function affecting the mental state and possibly consciousness of patients due to an external force (Menon et al., 2010). mTBI is difficult to diagnose because patients typically lack apparent external injuries and clear pathological findings in conventional computed tomography and magnetic resonance imaging (MRI) scans (Tarapore et al., 2013), although evidence of microscopic MRI-based morphological changes has been recently reported (Pasternak et al., 2014; Sasaki et al., 2014). Symptoms, such as headaches, fatigue, and dizziness (Cassidy et al., 2004) usually emerge on the day of injury and persist for a few days following injury (Boccaletti et al., 2006), but in most patients, symptoms resolve and cognition recovers within three months. However, up to 25% of patients (Sigurdardottir et al., 2009) suffer residual symptoms, long-term impairment, and sometimes disability (Levin 2009). Traumatic brain injury is a major cause of sustained morbidity and disability both in the military and civilian populations (Tarapore et al., 2013), as repeated mTBI can cause a wide range of neurological and cognitive deficits affecting memory, reasoning, language, and emotions (NINDS, 2002).

In the last two decades, a plethora of studies has attempted to characterize the structural and functional effects of mTBI (Eierud et al., 2014). Of particular interest are studies of resting state neurophysiological recordings, obtained using Electroencephalography (EEG) and Magnetoencephalography (MEG), because they require no training or experience with cognitive tasks, and they impose minimal demands on a patient, which is especially important after brain injury. One of the very first studies using resting-state MEG as a possible biomarker for mTBI showed that functional connectivity could be a valuable tool for early detection of mTBI (Zouridakis et al., 2012). Other studies showed abnormal slowing in brain areas affected by TBI (Huang et al., 2014) and reduced overall functional connectivity in TBI patients compared to controls (Tarapore et al., 2013). In particular, resting-state MEG source imaging (Huang et al., 2012) was able to detect abnormalities in mild and moderate TBI with 87% and 100% accuracy, respectively. Furthermore, combining MRI with MEG (Lewine et al., 1999) could discriminate between healthy adults and individuals with resolved mTBI. Compared to healthy controls, mTBI subjects showed reduced complexity in multiple brain areas (Luo et al., 2013). Decreased connectivity in resting-state MEG may persist for years after mTBI (Castellanos et al., 2011), but the abnormally reduced connectivity might improve over time (Tarapore et al., 2013).

Continuing our earlier attempts to understand how mTBI affects communication networks in the human brain (Zouridakis et al., 2012, Pollonini et al., 2010, Dimitriadis et al., 2015), in this study, we employ recordings of resting-state EEG and MEG and power spectrum analysis at the source level to investigate abnormalities in brain activation profiles of mTBI patients.

II. Materials and Methods

A. Subjects

Six mTBI subjects (4 male, 2 female, average age 28.3±7.3) and five orthopedic controls (3 male, 2 female, average age 29.4±7.4), i.e., subjects with minor orthopedic/extremity injuries who did not sustain head injury were recruited for this study. All data were obtained at the Huntington Medical Research Institutes, Pasadena, CA, USA. Exclusion criteria included a personal history of neurological or psychiatric illness, neurological disorders, serious medical condition,

M. Pagnotta and L. Li are with the Biomedical Imaging Lab, University of Houston, Houston TX, USA.

X. Arakaki, T. Tran, D. Strickland, and M. Harrington (mghworks@hmri.org) are with Huntington Medical Research Institutes, Pasadena, CA.

G. Zouridakis (zouridakis@uh.edu; phone: +1-713-743-8656; FAX: +1-713-743-0172) is with the Departments of Engineering Technology, Computer Science, and Electrical & Computer Engineering, University of Houston, Houston, TX 77204, USA.

and drug or alcohol addiction. The protocol was approved by the appropriate institutional review board, and written informed consent was obtained from all participants in the study.

B. EEG and MEG Recordings and Signal Preprocessing

Subjects were asked to remain as still as possible during the recording procedure and keep their eyes open.

Approximately 5 minutes of continuous EEG activity was acquired from each subject using a dry electrode EEG system (Wearable Sensing, San Diego, CA). The system includes 21 channels for EEG and two additional channels to record EOG and EKG activity to monitor eye and cardiac artifacts. Data were collected at a sampling rate of 300 Hz.

Furthermore, 5 minutes of continuous MEG activity was acquired from each subject using a CTF MEG system (MEG International Services Ltd., Coquitlam, BC, Canada). This whole-head system includes 66 axial gradiometer sensors and 31 additional channels that can be used for noise reduction. Data were collected at a sampling rate of 625 Hz and bandpass filtered between 0.1–200 Hz using hardware.

All data analyses were done in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States) using Brainstorm (Tadel et al., 2011) and in-house software developed in the Biomedical Imaging Lab at the University of Houston. Both the EEG and MEG sensors were co-registered with an anatomical MRI template (Colin27) using six fiducial references, the nasion, left pre-auricular point, right pre-auricular point, anterior commissure, posterior commissure, and an interhemispheric point. All results were visually inspected for accuracy.

A detrending procedure was applied to all EEG and MEG recordings to remove linear trends. Additionally, data were bandpass filtered between 0.1-80 Hz, whereas line noise was removed using a 50 Hz notch filter. Eye blink artifacts were removed using the additional eye channel signals and an automatic eye blink detection procedure based on signal-space projection. The identified eye activity topographies were visually inspected for accuracy. At least 2 minutes of artifact-free EEG/MEG activity was necessary for a subject to be included in final analysis.

C. Intracranial Source Power Analysis

A BEM (boundary element method) head model was used for the EEG/MEG forward calculation. Three layers of tissues representing the scalp, outer skull, and inner skull were extracted from a reference MRI (Colin27), using 1922 vertices per layer and 4 mm of skull thickness. The grid of dipolar sources was defined on the reference MRI cortex surface and consisted of approximately 15,000 vertices. The lead field matrix was computed using the overlapping spheres method (Huang et al., 1999).

Estimation of intracranial sources for each subject was performed using the dynamical Statistical Parametric Mapping (dSPM) procedure (Dale et al., 2000), which is based on whitened minimum norm estimation (wMNE), a depth-weighted linear L2 minimum norm estimation algorithm inspired from the original MNE method (Hämäläinen et al., 1994) and related software[1] (MNE manual, section 6). The dSPM value at each location is equal to the wMNE value divided by the projection of the estimated noise covariance matrix onto each source point. After whitening, the operational noise covariance matrix is by definition the identity matrix, and hence the projection of the noise is equal to the L2 norm of the row vector of the wMNE inverse operator (in the case of fixed dipole orientations).

More specifically, given a set of EEG/MEG surface recordings x(t), the relationship between the intracranial dipole sources s(t) and the EEG/MEG data x(t) is given by the so called *forward solution,*

$$\mathrm{x(t)} = \mathrm{A\,s(t)} + \mathrm{n(t)}, \qquad (1)$$

where s(t) denotes a vector of dipole component strengths, A denotes the linear forward matrix operator, and $n(t)$ denotes additive noise (Dale and Sereno, 1993). Assuming that the prior information about dipole strength follows a multivariate Gaussian distribution, the maximum a posteriori probability estimate is given by

$$\hat{s}(t) = Wx(t), \text{ with } W = RA^T(ARA^T + C)^{-1}. \qquad (2)$$

W is the inverse operator, $C = < n(t)n(t)^T >$ is the data noise covariance matrix, and R is the spatial covariance matrix of the dipole strength vector. The variance of each dipole strength estimate due to the additive noise $n(t)$ is given by

$$var(\hat{s}_i) = < (w_i n(t))^2 > = w_i C w_i^T, \qquad (3)$$

where $\hat{s}_i$ denotes the i^{th} element of the dipole strength vector $\hat{s}$ and w_i is the i^{th} row of the linear inverse operator W.

In the case of fixed dipole orientations, for each time point t and location i, a noise-normalized activity estimate $\hat{s}_{n,i}(t)$ can be computed by dividing the total dipole strength estimate in location i by the predicted standard error of the estimate due to the additive noise, using the formula

$$\hat{s}_{n,i}(t) = \frac{\hat{s}_i(t)}{\sqrt{w_i C w_i^T}} = \frac{w_i \cdot x(t)}{\sqrt{w_i C w_i^T}}. \qquad (4)$$

For source reconstruction, we used the recordings obtained from all sensors. A pre-whitening transformation was applied to the data to pre-scale the channels using the noise covariance matrix. Furthermore, we selected constrained source orientation, which considers that at each vertex of the cortex surface there is only one dipole whose orientation is normal to the surface at this point.

Power spectral density (PSD) analysis based on Welch's method was performed on all source estimates, using a window length of 2 sec with 50% time overlap. The EEG/MEG frequency bands of interest were the following:

[1] http://www.nmr.mgh.harvard.edu/meg/manuals/MNE-manual-2.7.pdf

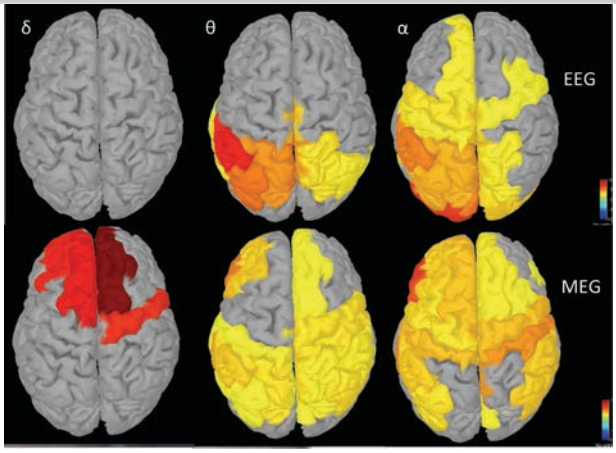

Fig. 1 Statistically significant differences in activation profiles (z-scores) between mTBI and control subjects in the lower frequency bands, for EEG (top) and MEG (bottom).

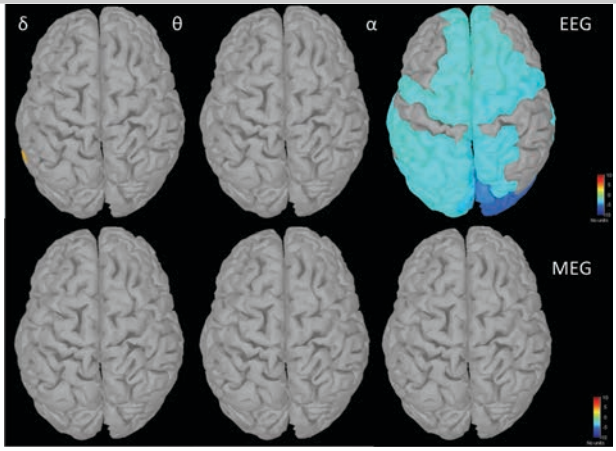

Fig. 2 Statistically significant differences in activation profiles (z-scores) between a control subject and the normative database in the lower frequency bands, for EEG (top) and MEG (bottom).

0.1-4 Hz (delta), 4-8 Hz (theta), 8-10.5 Hz (alpha1), and 10.5-13 Hz (alpha2). For higher frequencies, 13-20 Hz (beta1), 20-30 Hz (beta2), 30-40 Hz (gamma1), and 40-80 Hz (gamma2) were selected.

The Desikan-Killiany atlas (Desikan et al., 2006) defined in the FreeSurfer software was used for common co-registration of sources. This atlas consists of 34 brain regions of interest (ROIs) for each hemisphere and it is available as a free download online[2]. After averaging the power estimates across all vertices belonging to the same ROI, a map of 68 ROIs by 8 frequency bands was obtained for each subject.

D. Normative Database and z-score Maps

We further defined a *normative database* using all five datasets from the control group, separately for the EEG and MEG recordings. Specifically, averaging the power maps across the five control subjects yielded two matrices (68 × 8, ROIs-by-frequency bands), one with the mean values and a second one with the standard deviations, for each frequency band. The same estimation procedure was followed for each mTBI subject.

Each patient was compared to the normative values, and for each ROI assessed, a z score was computed using the following expression:

$$z_{ij} = \frac{P_{ij} - Mean_{ij}^{C}}{SD_{ij}^{C}}, \text{ with i = 1, 2 … 68, j = 1, 2, … 8,} \quad (5)$$

where P_{ij} is the ij element of the power map and $Mean_{ij}^{C}$ and SD_{ij}^{C} are the mean and standard deviation values, respectively, from the two normative database matrices corresponding to the i-th ROI and j-th frequency band (Huang et al., 2012).

E. Statistical Thresholding

To identify statistically significant z-scores we used alpha = 0.05 and false discovery rate correction (Benjamini & Hochberg, 1995) for the 544 (68 × 8) multiple comparisons, resulting in a threshold value of 2.2421. After thresholding, the statistically significant z-scores were projected onto the Desikan-Killiany atlas (Desikan et al., 2006) using different colors for each z-score value to visualize the brain areas that differed significantly between the two groups.

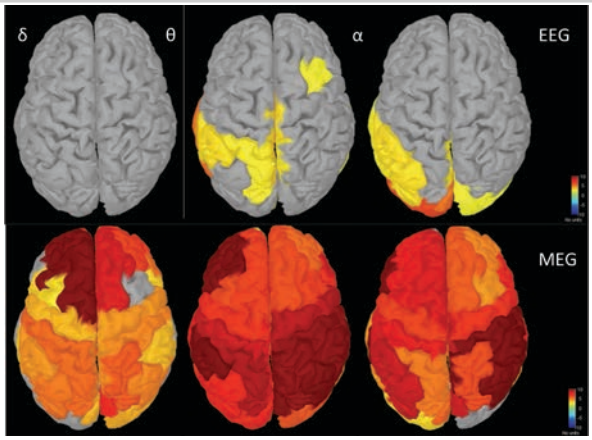

Fig. 3 Statistically significant differences in activation profiles (z-scores) between an mTBI patient and the normative database in the lower frequency bands, for EEG (top) and MEG (bottom).

III. Results

When comparing the mTBI and control groups, statistically significant differences in the form of overactivation were seen primarily in the theta (4-8 Hz) and low alpha (8-10.5 Hz) bands for the EEG and the delta (0.1–4 Hz), theta (4-8 Hz), and low alpha (8-10.5 Hz) bands for MEG data, as shown in Fig. 1.

To test the power of the methodology to correctly classify subjects on a single subject basis, we used the first four controls to construct the normative database, while the fifth one was used to construct the activation maps (z scores) shown in Fig. 2. For comparison, Fig. 3 shows the activation maps of one mTBI subject. These figures show that the control subject does not differ significantly from the

[2] http://surfer.nmr.mgh.harvard.edu/

normative database, while the mTBI subject shows significant differences mostly in the lower frequency bands. Additionally, the MEG modality seems to more accurately characterize the individual subject group.

Overall, even though the number of participants is small at this early stage of the study, the results obtained suggest that analysis of resting-state EEG and MEG activation maps is a powerful tool that can help in the diagnosis of and assess the efficacy of intervention in mTBI.

Acknowledgment

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